## REMARKS

### I. Status of the Claims

**Claims 62-69 are pending.** Claim 62 has been amended to delete the phrase "or to affect said desired phenotype". New claim 69 has been added. This claim incorporates the limitations of claims 66 and 68. Support for the transcriptional regulatory sequence being a promoter is found in Applicants' specification on page 7, third full paragraph. Accordingly, no new matter has been added with the amendments.

### II. Miscellaneous

#### A. Priority

On page 2 of the Office Action, the Examiner asserts that the priority filing date is being assigned to U.S. Application 09/276,820, filed March 26, 1999. The Examiner asserts on page 2 that he cannot decide what part of the specification was added or deleted in each application because "the specification has been substantially altered." The Examiner requests that Applicants point to support in Applicants' earlier listed priority applications, including U.S. Applications 09/263,814, filed March 8, 1999, 09/253,022, filed February 19, 1999, 09/159,643, filed September 24, 1998, and 08/941,223, filed September 26, 1997. First, Applicants point out that each of the priority applications is available in the Patent Office. The Examiner should be able to

review each of these to determine when the claimed invention in this restriction group was disclosed. Nevertheless, Applicants have reviewed the applications. The claimed invention was first disclosed in U.S. Application 08/941,223 (see, e.g., 9:11-14; 12:25-30; 43:23-30 through 44:1-4; 45:22-25).

B. Sequence Listing Requirements

On page 2 of the Office Action the Examiner asserts that the application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825. Specifically, the Examiner asserts that the specification discloses amino acid sequences in Figures 14-16 and 29-35 but that these sequences are not identified by sequence identifiers in the patent application. Accordingly, Applicants have amended the specification.

C. Specification

On page 3 of the Office Action, the Examiner objects to the Abstract as being unduly lengthy. Applicants will amend the Abstract when the substantive issues have been resolved.

The Examiner also asserts that text is missing in lines 10 and 11 on page 130, line 22 on page 134 and line 30 on page 140. Applicants have made the appropriate correction.

## III. **Rejections**

### A. Rejection Under 35 U.S.C . § 112, First Paragraph; Written Description

On page 4 of the Office Action, claims 62-68 are rejected under 35 U.S.C. § 112, first paragraph, on the grounds that they contain subject matter "which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, have possession of the claimed invention". Applicants respectfully traverse the rejection.

The position taken by the Examiner is that the claim constitutes a "genus" claim because the claim encompasses a genus of compounds. He asserts that the claim lacks adequate written description because compound structure is an essential component, the specification does not describe a generic structure for a compound, the genus of compounds lacks written description, and, therefore, the claim lacks written description. The Examiner cites the Guidelines On Written Description, published January 5, 2001, in the Federal Register, Volume 66, No. 5, page 1099-111. Applicants submit that the Examiner's application of the Guidelines does not apply to the claimed methods. The novelty is in the method steps and not in the specific compound to be tested.

The structure of a compound is not essential to the claimed methods. The methods do not depend upon the compound having any particular structure. The methods are directed only to *testing* a compound to see if the compound has any activity. Thus, there is no limitation on the compound to be tested.

Many compounds will fail to have an effect. Nevertheless, Applicants' methods can be used to determine if a given compound has an effect. Thus, the methods are adequately supported for a genus that comprises the universe of all testable compounds regardless of structure.

This point was discussed in an interview held on April 17, 2002, with Examiner Shukla, Dr. Youssef Bennani, Director of Medicinal Chemistry at Athersys, Inc., and Anne Brown, Applicants' attorney. Dr. Bennani explained how the drug discovery process is practiced in the industry and that for the generation of hit compounds it is conventional to test compounds selected at random. The Examiner is directed to the Declaration submitted with this Response. See point 3.

Dr. Bennani, the Declarant, explains that (1) the process of drug discovery relies on the testing of a multitude of compounds with a multitude of structures and characteristics in order to discover those compounds that qualify as "hits" (compounds that are potential modulating agents with the potential to have therapeutic value); (2) such

a "hit" is the starting point for drug development in that the hit provides a compound that might have to be optimized (structure modified) to form a "lead" compound which may then be further optimized and tested for efficacy and safety; (3) it was conventional in the art to randomly select compounds for testing from large numbers and varieties of compounds.

In the Office Action the Examiner cites U.S. Patent No. 6,159,705. This patent contains "genus" claims directed to contacting a cell with a test compound to identify a compound that modulates a receptor. The disclosure for this patent, based on the Examiner's analysis, would not meet the written description requirement. First, the Examiner states that Applicants' specification does not disclose a representative number of species *described by their complete structure*. This is not found in the '705 patent either. The '705 patent specification contains the structures for a few small peptides. Other than that there is only general disclosure of the myriad types of compounds that might be selected, but no structural information of the kind required under the Guidelines (where compound is critical). See 3:12-35; 4:3-8; 8:41-48; 11:4-42; 39-43:62 in the '705 patent. Applicants do not suggest that the '705 patent specification is deficient. Applicants suggest that to practice the claimed method in the '705 patent and in Applicants' application, the structure of compounds is not a critical consideration.

Applicants point out that claims of this type, where the specific structures of compounds are not known, are issued as a matter of current policy in the U.S. Patent and Trademark Office. Applicants refer to the attached Appendix A which was distributed on March 19, 2002, at a Biotechnology/Chemical/Pharmaceutical Customer Partnership Seminar. Brian Stanton explained that the requirements listed by the Examiner must be met in order to obtain claims directed to the *compounds themselves* but that the Applicant can still obtain a claim for compound testing in the absence of generic structural information . See page 5 of the Appendix, where it is indicated that the scope of protection extends to screening assays even where the structure of the compounds is not disclosed.

The Appendix shows slides directed to exemplary reach-through claims. The exemplary target is a receptor. However, the policy is based on a legal rationale that extends the scope of protection to claims for a method of screening against other protein targets. There is no legal reason, and the PTO policy does not present one, why the PTO would grant claims to methods for screening for agonists and antagonists of receptors and not for agonists and antagonists of other gene products. The fact that the target is a receptor does not impose a specific structure on any of the compounds to be tested in drug discovery. Therefore, receptors are not an exception to the rule but simply illustrate the rule.

For these reasons, Applicants submit that the claim is adequately supported in the specification and, as a matter of policy, should meet the requirements imposed by the U.S. Patent and Trademark Office in the Written Description Guidelines.

In view of the above discussion, Applicants submit that the grounds for rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. Rejection Under 35 U.S.C. § 112, First Paragraph; Enablement

On page 5 of the Office Action, claims 62-68 are rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the claims are not enabled. Applicants respectfully traverse the rejection.

First, the Examiner bases the rejection on the assumption that the Applicants have not enabled any vector for activating an endogenous gene except a vector containing a promoter or enhancer. Applicants respectfully disagree. There are various known ways to regulate gene expression besides modification of a promoter or enhancer. These are disclosed in Applicants' specification, for example, on page 46, lines 8-11. These elements are known in the art to function as transcriptional control elements.

Accordingly, contrary to the Examiner's assertion, the specification enables vectors that contain transcriptional control elements other than promoters and enhancers.

As a further ground for the rejection, on page 7, the Examiner asks "What is drug screening or is the claimed method a method of drug screening?" Applicants point out that the preamble of the claim is directed to a method for "drug discovery" because compound screening is a step in the drug discovery process. In the drug discovery process, as discussed above and in the Declaration, an initial step is screening a compound for its effect. A positive hit may or may not turn out to be a "drug" as defined in the Examiner's Office Action on page 7. A hit compound can be optimized with respect to structure and used to form a "lead" compound. Dr. Bennani discusses this point in the Declaration. See point 4.

The Examiner also objects that "the steps of the claimed invention do not represent in any way a method of treatment, diagnosis, alleviation or prevention or cure of disease". The Examiner is correct. The method is not a method of treatment. It is a method of discovering a compound that has an effect on gene expression. This provides a compound that may succeed or fail at providing the effects of a drug. It may turn out to meet the definition of "drug" or may provide a substrate for optimization (i.e. drug development).

The Examiner further objects that "...by practicing the claimed method an artisan of skill would not be able to determine whether a compound that was isolated by the claimed screening method would have any of the properties of a drug". It is unclear how the Examiner reaches this conclusion. A compound that affects expression is a drug candidate. Whether it will be a successful drug requires further testing. This is done conventionally with any compound that is a drug candidate. The majority of marketed drugs were developed using this process. The drug discovery industry has produced scores of drugs based on initial compound screening, hit optimization, lead optimization, and routine pre-clinical and clinical testing. Further, it is not necessarily by practicing the claimed method that one can determine whether a compound is a drug. By practicing the claimed method one discovers a compound that will have an effect on a target gene or target phenotype. As discussed above, this is one discrete and useful step in the drug development process.

In summary, the claimed process itself provides a useful method for identifying a compound that affects a desired target gene or phenotype. Applicants point out that the claim is limited to determining the ability of the compound to interact with the product of the desired activated gene or to affect a desired phenotype. Accordingly, the specification need not teach how to determine therapeutic effects of the compound in steps that form the basis for other stages of the drug discovery process.

As further grounds for the rejection, the Examiner queries what compounds "can be used in the instantly claimed method". See page 7, paragraph spanning pages 7 and 8. Again, Applicants point out that the exact nature of the compounds is not relevant to practice the claimed method. The method simply calls for testing ANY GIVEN COMPOUND.

The Examiner goes on to argue (page 9) that the specification does not provide guidance as to what criteria are used to select one or more test compounds, what the structure of the compound would be, or what the characteristics of the compound would be. As discussed above, in the drug discovery art, any compound available in the art is a candidate for screening.

The Examiner also asserts, on page 8, that all of the steps of the method have not been disclosed at one place. Applicants respectfully submit that the person of ordinary skill in the art would have understood from the term "drug discovery" steps that MUST be used for drug discovery with RAGE-activated cells. Thus, the steps are inherent and would have been immediately recognized by the person of ordinary skill in the art of drug discovery. Support need not be *ipsa verbis* (explicit) as long as the specification reasonably conveys the claimed steps. If by the term "drug discovery" the person of ordinary skill would recognize how this is conventionally done, then the claim is adequately described so that the artisan can practice the method as claimed. This issue is

also addressed in the Declaration. Dr. Bennani states that the claimed steps are implicit in cell-based drug discovery. See point 5.

On page 8 of the Office Action, the Examiner refers to U.S. 6,159, 705. The Examiner indicates that drug discovery using homologously recombinant cells is enabled but drug discovery using non-homologously recombinant cells is not enabled. He states "therefore, the artisan would have prior knowledge of the gene products of the endogenous activated and [gene] therefore would be able to perform steps d and e." He then concludes,

> However, in the instant case, an artisan *does not have any knowledge what gene has been activated* and therefore, step c is to be carried out to find a cell in which a desired gene has been activated. But it should be emphasized that even when a cell in which a desired gene is activated, [sic] there is no way of knowing if the desired phenotype observed in a selected cell is due to activated expression of only the desired gene or due to a activated [sic] of multiple genes.

Emphasis added.

With regard to this specific argument, Applicants point out that it was already made (under § 112, first paragraph) in the very first Office Action, dated April 28, 2000. This issue was resolved in an interview following the final Office Action dated November 17, 2000. Examiner Priebe indicated that use of the term "desired", with reference to the activated gene or phenotype, would resolve the issue. Accordingly,

Applicants amended the claim to insert this term and agreed to refile the case. The Examiner then withdrew the rejection under § 112, first paragraph. Applicants, therefore, submit that this specific issue has been resolved and this ground of rejection should be withdrawn. For the Examiner's convenience Applicants provide, as attached Appendix B, the April, 2000 Office Action in which this ground of rejection was set forth. See, specifically, the text highlighted on page 4.

The Examiner then indicates that the phenotype of the treated cell must be compared with the phenotype of a non-treated cell and the specification does not describe this step. Applicants respectfully disagree. To determine if there is an effect implies a comparison before and after treatment. This need not be explicit since the person of ordinary skill in the art would understand "determine an effect" to mean that they must "ascertain this change."

In the view of the above discussion Applicants submit that all of the grounds for rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

C. Rejection Under 35 U.S.C. § 112, Second Paragraph

On page 10 of the Office Action, claims 62-68 have been rejected on the grounds that they are indefinite. Applicants respectfully traverse the rejection.

The Examiner first rejects the claims for being indefinite asserting that "said one or more cells" in line 1 of step c has insufficient antecedent basis. Applicants submit that the term "one or more cells" in step c has perfect antecedent basis in line 2 and line 3.

On page 10 of the Office Action, claims 62 and 63 have been rejected on the grounds that it is unclear whether the desired gene recited in step c is the same as the activated gene recited in step b. Applicants point out that in step a, an endogenous gene is activated in one or more cells. Step c is merely directed to screening for a desired gene or phenotype. However, step d requires that a cell in which a desired gene is activated is actually produced. Accordingly, it is clear that the desired gene is the result of one of the activation events in step a.

On page 10 of the Office Action, claim 62 is rejected on the grounds that is incomplete because it omits an essential step. The Examiner asserts that the omitted step is a sub step of step c where the desired phenotype in the cell expressing the activated gene is compared with another cell where the vector is not integrated. Applicants

respectfully submit that step c inherently covers screening for a phenotype that did not exist in the parental cell before the vector was integrated.

There are many steps that could be considered critical but which would be understood as included in the method. For example, cells must be added to the culture medium before they can be cultured but there is no requirement that the step of adding the cells to the culture medium be explicitly recited. Similarly, cells must be transfected with a vector before it integrates. Thus, any number of "critical" steps could be added. However, legally, this is not required. Applicants need to point out the invention, not every conceivable step that is involved in the laboratory.

Another "critical" step that the Examiner asserts is omitted is a comparison of the effect of the test compound on a cell where a desired gene is activated with the effect on a cell in which the desired gene is not activated, i.e., the parental cell. Actually, this is incorrect. What is ascertained is the effect on expression of the desired gene. Therefore, the "comparison" would be the cell expressing the gene before the compound is added. That is the only way to see the "effect". Note that the claim only calls for testing the compound with the activated gene or with the activated phenotype. Accordingly, there is no reason to expose the parental non-activated cell to the compound.

Claim 63 is rejected for the same reasons (allegedly omitting essential steps). Applicants submit that this rejection is also improper. The test compound is merely exposed to the secreted protein. To determine if a compound can interact with a secreted protein, one simply produces the protein, exposes it to a compound, and measures interaction. If any comparison is to be done, it would be the secreted protein before and after exposure to the compound.

In view of the above discussion, Applicants submit that the grounds for rejection have all been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

D. The Rejection Under 35 U.S.C. § 102

On page 11 of the Office Action, claims 62 and 66 are rejected under 35 U.S.C. § 102(e) on the grounds that they are anticipated by U.S. Patent No. 6,159,705, herein "the '705 patent". Applicants respectfully traverse the rejection.

First Applicants point out that claim 62 has been amended to delete the phrase "or to affect said desired phenotype". Applicants delete this phrase without prejudice or disclaimer and reserve the right to file one or more continuation applications directed to the deleted subject matter.

On page 11 of the Office Action, the Examine cites the specific text upon which the rejection is based. The Examiner states that column 45, lines 63-67, shows that the endogenous promoter of a yeast cell can be replaced by homologous recombination with a Bar1 promoter engineered to cause higher levels of expression of Bar1 upon pheromone stimulation. The Examiner then concludes that the reference "teaches a method of screening for compounds that alter the expression of an endogenous gene wherein the expression of the endogenous gene is activated by altering the endogenous promoter of the endogenous gene by homologous recombination". Accordingly, the Examiner concludes that the '705 patent anticipates the invention of claims 62 and 66. Applicants respectfully submit that the text cited by the Examiner, as well as the remainder of the reference, does not anticipate Applicants' claims 62 and 66 because there is no disclosure or suggestion that the test compound would interact with the activated gene product.

The Examiner's cited embodiment and the rest of the reference teach that the endogenous gene that is activated is an *indicator* gene. It indicates that the signal transduction pathway has been activated. The pathway is activated by a receptor. The receptor is activated by an agonist. Therefore, activation of the indicator occurs only if an agonist acts on the receptor. The receptor is a heterologous gene, as the Examiner notes on page 11 of the Office Action. The heterologous receptor is functionally linked to an endogenous signal transduction pathway. The indicator gene has a heterologous

promoter that is responsive to the signal transduction pathway. The end result is activation of the indicator gene. Thus activation of the indicator indicates agonist activity for the test compound.

Applicants point out that the test compound interacts with the receptor and not with the indicator gene. The promoter that is linked to the indicator gene is used to increase the ease of detection of indicator activity by increasing the amount of indicator gene product. Thus, in the text example cited by the Examiner, an engineered promoter, derived from a Bar1 promoter, engineered to be more active than a native promoter, is linked to an endogenous indicator gene, the Bar1 gene. An agonist causes the receptor to activate the signal transduction pathway (in this case pheromone responsive pathway), which ultimately acts at the engineered promoter to cause expression of the Bar1 indicator gene. Accordingly, there is no disclosure or suggestion that the test compound would or should interact with the indicator gene product, the Bar1 protein, itself. Applicants' claim 62, however, recites that the test compound interacts with the activated gene. Therefore, Applicants' present claims 62 and 66 are not anticipated by the '705 patent.

Applicants note that previous claim 68 was not rejected over this art. Claim 68 was directed to the embodiment wherein the vector integrates into the genome by non-homologous recombination. Accordingly, claim 69, which incorporates the

limitation of claim 68, should not be anticipated by this reference for the Examiner's reasons of record.

Next, the Examiner indicates that the claimed method encompasses both homologous and non-homologous recombination but that the specification does not enable non-homologous recombination. The inference is that the reference used to reject the claims is enabled because it practices the method of drug discovery on cells made by homologous recombination.

It is unclear why drug discovery methods are enabled with homologously recombinant cells but not with non-homologously recombinant cells. In other words, compounds can be tested on a desired gene product and against a desired phenotype irrespective of whether this phenotype or gene product is generated by an exogenous coding sequence, by an endogenous coding sequence in a homologously recombinant cell, or by an endogenous coding sequence in a non-homologously recombinant cell . No matter how the gene is expressed, a compound that will affect gene expression can still be identified in any of these cells.

In view of the above discussion, Applicants respectfully submit that the grounds for rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, requested.

If the Examiner believes that a telephonic interview would expedite prosecution of this case, he is invited to contact Applicants' attorneys, Anne Brown, at 216-426-3586, or Joseph Contrera at 703-683-6197.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Amended Claims with Marking to Show Changes Made"**.

Respectfully submitted,

Anne Brown

Anne Brown
Registration No. 36,463

Shanks & Herbert
TransPotomac Plaza
1033 N. Fairfax Street #306
Alexandria, VA 22314
Phone: (703) 683-3600
Fax: (703) 683-9875

## VERSION WITH MARKINGS SHOWING CHANGES MADE

**In the Specification:**

On page 29, beginning at line 19, lines 19-25 have been replaced with the following lines:

**FIG. 29A-29B.** Nucleotide sequence of pRIG14. (SEQ ID NO: 21).

**FIG. 30A-30C.** Nucleotide sequence of pRIG19. (SEQ ID NO.: 22).

**FIG. 31A-31C.** Nucleotide sequence of pRIG20. (SEQ ID NO.: 23).

**FIG. 32A-32C.** Nucleotide sequence of pRIGad1. (SEQ ID NO.: 24).

**FIG. 33A-33D.** Nucleotide sequence of pRIGbd1. (SEQ ID NO.: 25).

**FIG. 34A-34B.** Nucleotide sequence of pUniBAC. (SEQ ID NO.: 26).

**FIG. 35A-35B.** Nucleotide sequence of Prig22. (SEQ ID NO.: 27).

Please put a period after the text in lines 10 and 11 on page 130 as follows:

(g) Incubate at 4°C (hold).

(h) END.

Please put a period after the text in line 22 on page 134 as follows:

(ii) 30 cycles of 92°C denaturation for 15 sec; 60°C primer annealing for 20 sec; and 72°C primer extension for 40 sec.

Please put a period after the text in line 30 on page 140 as follows:

35) After binding collect SA-PMPs through use of a magnet and recover flow through

material (SAVE THIS MATERIAL!).

In line 26, page 140, after "add" please substitute -- the -- for "he" as follows:

33) Purifying the products of the second strand reaction using the PCR cleanup kit from

Qiagen. Elute in 50 µl EB and add the products of ~~he~~ the second strand reaction to 150 µl

of the PMPs.

**In the Claims:**

The claims are amended as follows:

62. A method for drug discovery comprising:

(a) integrating a vector into the genome of one or more eukaryotic cells, wherein said vector integration activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds to be screened for drug activity; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene ~~or to affect said desired phenotype.~~